Relapsing disease is still the major cause of treatment failure. Additional strategies, such as maintenance therapy with novel agents or judicious use of donor lymphocyte infusions merit further investigation for converting PR to CR and reducing relapse risk.

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THE GRAFT-VERSUS-MYELOMA EFFECT USING NON-MYELOABLATIVE OR REDUCED INTENSITY ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

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Following myeloablative conditioning due to high treatment-related mortality (TRM), some studies have shown an inferior outcome using allogeneic HSCT compared to autologous transplant. More recently, non-myeloablative (NMA) and reduced intensity conditioning (RIC) for allogeneic HSCT was introduced. A prerequisite for this approach is a significant graft-versus-myeloma effect, which has not clearly been demonstrated. Between 1997 and 2005, 177 patients were reported to the CIBMTR following NMA (n = 120) or RIC (n = 57) and an allogeneic HSCT from an HLA-identical sibling donor. Median age was 50 years (range 24-69). Planned tandem autologous transplant followed by allogeneic HSCT was given to 105 of these patients. Most patients were given peripheral blood stem cells (98%). Outcomes, with a median follow-up of 55 months (range 3-98) and 25 months (range 3-76) respectively for allogeneic HSCT and autologous transplant followed by allogeneic HSCT, see Table below.

The following variables were significant in univariate outcomes analyses and were therefore used in the multivariate modelling: age, sex, performance status, IgG vs. non IgG myeloma, disease status and chemosensitivity, prior lines of chemotherapy, donor-recipient sex match, NMA vs. RIC, year of transplant and GVHD as the time dependent covariate. The only factor on multivariate analysis that increased the risk of TRM was acute GVHD (RR 2.38, p = 0.018). Only chronic GVHD decreased the probability of relapse on multivariate (RR 0.43, p = 0.012), but this effect was not seen in patients with IgG myeloma (n = 97, RR 0.7, p = 0.3) in comparison to all other types of myeloma (n = 80, RR 0.11, p = 0.004). Improved PFS was associated with autologous + allogeneic HSCT (RR 3.6, p = 0.001) and absence of acute GVHD (p = 0.001), but not chronic GVHD (RR 0.9, p = 0.7). In conclusion, patients receiving allogeneic HCT for myeloma, chronic GVHD decreased the probability of relapse, but only in patients with non-IgG myeloma. PFS was improved in patients receiving autologous + allogeneic HCT and was decreased in those with acute GVHD.

Outcomes	Allo only	Auto + Allo
Number of patients	72	105
Acute GVHD at 100 days, grades (1-4)	47 (37-60)%	37 (28-46)%
Chronic GVHD at 3 years	55 (43-67)%	58 (43-72)%
Treatment Related Mortality (TRM) at 3 years	27 (17-38)%	16 (10-25)%
Relapse at 3 years	48 (36-60)%	41 (29-54)%
Progression-free survival (PFS) at 3 years	25 (15-37)%	42 (20-43)%
Overall Survival at 3 years	45 (33-58)%	64 (53-75)%

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PHENOTYPIC ANALYSIS OF MULTIPLE MYELOMA CELL PROGENITORS

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The lack of specific molecules to define the multiple myeloma (MM) malignant cells responsible for disease development and relapse has hampered the evaluation of minimal residual disease (MRD) in MM. PC development compromises an array of subpopulations with distinctive phenotypes. Syndecan (CD138) is expressed in plasma cells (PC) and studies using CD138+ selected cells may be problematic since earlier progenitors may be excluded. To define myeloma bone marrow (BM) progenitor phenotype we developed a multicolor flow cytometry assay to study them. We have identified a CD138- subset that co-express CD19+, CD27+ and identical kappa or lambda light chain restriction as the abnormal plasma cells, as previously shown by others. Further characterization has shown that this subset co-expresses the c-Kit (CD117) (20%) and Notch-1 receptors (90%) as the hematopoietic stem cells (HSC) CD34+ counterpart. A small percentage of this BM cells show aldehyde dehydrogenase (ALDH) activity. Flow sorting of CD138- was feasible with 99% purity. Isolated populations were grown in methylcellulose with 5% PHA-leukocyte conditioned medium. CD138+ cells did not exhibit colony formation, and neither did the CD138-/CD38+/CD19-/CD34- cells. Instead, CD138-/CD38+/CD19+/CD34- cells were able to grow cell colonies (>100 cells) although their efficiency was low (1 in 15,000). CD34+ cells (HSC) also were able to grow cell colonies but with a significant lesser efficiency compared to SCF, IL-3 and GM-CSF cytokine stimulation. Cells harvested at day 14 from CD34+ and CD138-/CD38+/CD19+/CD34- generated colonies showed a lympho-plasmacytoid appearance. We showed that only CD138-/CD38+/CD19+/CD34- cells, but not CD34 + HSC, differentiated into a more mature syndecan (CD138+) expressing cell as determined by flow cytometry. Isolated CD138-/CD38+/CD19+/CD34- cells shown to be relatively bortezomib-resistant when compared to CD138+ plasma cells. The lacking expression of mature PC markers in this MM sub-population makes us hypothesize that they represent a progenitor B cells that differentiate into the malignant PC. Surrogate assays for stem cell activity (long term culture-initiating cell (LTC-IC), cobblestone-area forming cells (CAFC) and xenotransplant models should determine cancer stem cell activity of these cells. Research studies of these CD138- MM putative progenitor cells may lead to develop novel treatments to target MM subpopulations that may constitute the MRD reservoir.

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EFFICACY AND SAFETY OF CHEMOMOBLIZATION WITH VP-16 AND G-CSF IN PATIENTS (PTS) UNDERGOING AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) FOR MULTIPLE MYELOMA (MM)

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Introduction: Although the number of ASCTs performed for MM continues to increase, the optimal mobilization strategy remains unclear. Additionally, concern has arisen about the impact of age and prior lenalidomide exposure on mobilization efficacy. High dose etoposide has been previously shown to have antitumor activity and efficacy in progenitor cell mobilization, and has a favorable safety profile when cytokine is also given (Gianni et al., JCO 1992). Here, we report on the efficacy and safety of mid-dose etoposide and G-CSF as a mobilization regimen for pts with MM.

Methods: Between May 2004 and June 2009, 152 pts with MM underwent ASCT following the use of VP-16 (375 mg/m2 on D#1 and D#2) and G-CSF (5mcg/kg twice daily from D#3 through the final day of collection) for mobilization. 65 pts were female, 87 were male, and median age was 56 yrs (range 17-72). Collection was